REMARKS/ARGUMENTS

The Office Action states that claims 1, 6, 13, 22-23, 34-35, 45, 47, 49-52, 74-79, 100-105 and 113-126 are pending in the subject application. Further, according to the Office Action, claims 116-118 are allowed; claims 100-105, 113-115 and 119-126 are rejected and claims 1, 6, 13, 22-23, 34-35, 45, 47, 49-52, and 74-79 are withdrawn from consideration. Applicants respectfully submit, however, that claims 1, 6, 13, 22-23, 34-35, 45, 47, 49-52 and 74-79 were cancelled without prejudice or disclaimer, in applicants' Amendment mailed June 9, 1997 (filed June 16, 1997). Thus, only claims 100-105 and 113-126 are pending in the application.

Applicants have amended claims 113-115 to remove any alleged ambiguity regarding which polypeptides have the properties recited in the claims, as discussed below. Applicants maintain that the amendments to claims 113-115 do not raise any issue of new matter since the amendments merely involve minor formatting changes. Accordingly, applicants respectfully request entry of this Amendment. Upon entry of this Amendment, claims 100-105 and 113-126, as amended, will be pending and under examination.

Objection to the Specification

In ¶3 on page 2 of the Office Action, the Examiner objected to the disclosure because of certain alleged informalities, namely that page 32, lines 2-4, and page 53, lines 25-26, describe the hydrophilicity of the predicted protein sequence as allegedly

shown in Figure 16. According to the Examiner, however, Figure 16 does not describe hydrophilicity. The Examiner stated that appropriate correction is required.

In response, applicants have amended the specification to correctly identify Figure 15 as the figure showing the hydrophilicity of the predicted protein sequence. No new matter is added by this amendment, which is supported by Figure 15 of the application. Applicants respectfully submit that this amendment obviates the above-stated objection and request that the objection be withdrawn.

Applicants have also amended the brief description of Figure 15B to more accurately describe what is depicted in that figure. This amendment is also supported by the specification as filed and therefore no new matter is added to the application thereby.

Allowed Claims

Applicants acknowledge with appreciation the Examiner's statement in ¶10 on page 5 of the Office Action that claims 116-118 are in condition for allowance.

Claim Rejections under 35 U.S.C. §112, First Paragraph

Claims 113-115 and 119-126 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession

of the claimed invention. The Examiner stated that the amendment to these claims, filed January 19, 2001, Paper No. 26, Amendment G, recites an outside region of prostate-specific membrane antigen, the amino acid sequence of which outside region is set forth within SEQ ID NO:2 beginning with the amino acid number 45 at the amino terminus of the polypeptide. The Examiner further stated that he could find no support for this outside region, beginning with the amino acid number 45 at the amino terminus of the polypeptide, in the regions of the specification where applicants had identified support for this amendment to the claims. The Examiner stated that this is a new matter rejection.

In response, applicants respectfully traverse the Examiner's rejection. Applicants maintain that the term "outside region," read in light of the specification, clearly and unambiguously teaches the location of the "outside region" of PSM antigen. The amino acid sequence for the full length 100 kD PSM antigen is provided in SEQ ID NO:2. Applicants respectfully direct the Examiner to the following quotation from page 56, lines 5-11 of the specification which teaches that the PSM antigen is a membrane spanning protein and that the majority of the protein is exofacial, i.e., located in the "outside region":

> As the cDNA sequence implies that the antigen has the characteristics of a membrane spanning protein with the majority of the protein on the exofacial surface, antibodies, especially monoclonal antibodies to the peptide fragments exposed and specific to the tumor may provide for tumor imaging local extension of metastatic tumor or residual tumor following prostatectomy or

irradiation.

Ascertaining the location of the outside region is further facilitated by the teaching in the specification concerning the identification of the transmembrane domain. The transmembrane domain is disclosed as extending from amino acid #19 to amino acid #44 (page 53, lines 31 to 33). The location of this transmembrane sequence in relationship to the full amino acid sequence, easily deducible from the full sequence in SEQ ID NO:2, immediately permits localization of fragments of PSM antigen in the "outside region" which is defined as the larger portion of the protein.

Moreover, applicants note that specific embodiments of outside region fragments are disclosed in their specification, such as the fragments having SEQ ID NO: 35, 36, and 37, all of which are present in the portion of the sequence located on the carboxyl terminal side of the transmembrane domain sequence. Further support that such fragments are located on the outside region comes from the hydrophilicity plot in Figure 15, along with the teaching in the specification that the hydrophilic regions are located on the cell surface (page 31, lines 28-33). Fragments having SEQ ID NO: 35, 36, and 37 are disclosed as having the highest hydrophilicity (see page 31, line 33 to page 32, line 4; page 32, lines 24-27, and Figure 15B), and as such, must be located on the outside region of the PSM antigen.

In light of the above-described teachings, applicants respectfully submit that the rejection of claims 113-115 and

119-126 under 35 U.S.C. §112, first paragraph, is without merit. As demonstrated above, one of ordinary skill in this art, supplied with applicants' teachings, would readily understand from the specification as filed that the "outside region" of PSM antigen, recited in applicants' claims, is that part of the polypeptide sequence set forth within SEQ ID NO:2 beginning immediately after the transmembrane portion, which extends from amino acids 19 to 44, i.e., beginning with amino acid number 45 at the amino terminus.

Notwithstanding the Examiner's statement that he could find no support for the outside region beginning with amino acid number 45, applicants maintain that that the specification provides clear support for this definition of the outside region. Applicants therefore respectfully disagree with the Examiner's characterization of this rejection as a new matter rejection. The Examiner is therefore requested to reconsider and withdraw the §112, ¶1 rejection.

Claim Rejections under 35 U.S.C. §112, Second Paragraph

On page 3, ¶5 of the Office Action, the Examiner stated that claims 100-105, 113-115 and 121-126 are rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner asserted that claims 100-105 and 121 are indefinite because they do not recite the specific hybridization conditions which applicant[s] regard as being [necessary for] specifically hybridizing to a nucleic acid sequence of SEQ ID NO: 1. The

Examiner contended that whether or not specific hybridization occurs is a function of the hybridization conditions, including factors such as specific ionic strength, specific temperature and specific number of washings, and therefore the terms "hybridizes specifically" or "specifically hybridizes," as recited in the claims, encompass a variety of conditions which will vary depending on the nature of the specific nucleotide sequence structures which are being claimed, for example, depending on the length and G/C content of the sequences, and the number and amount of competing or similar sequences in a particular sample. The Examiner concluded that these claimed hybridizing sequences can be adequately defined only by specifically reciting hybridization conditions.

In response, applicants respectfully traverse the Examiner's rejection. With regard to claims 100-105 and 121, applicants respectfully point out to the Examiner that the term "specifically hybridizes" is a term of art which would be immediately understood by one of ordinary skill in the art, and further that one skilled in the art would readily be able to select appropriate conditions that permit specific hybridization of the probe recited in these claims to a nucleic acid encoding PSM antigen. Applicants note also that the term "specifically hybridizes" is defined in the specification of the subject application at page 23, lines 15-19, as "the ability of a nucleic acid molecule to recognize a nucleic acid sequence complementary to its own and to form double-helical segments through hydrogen bonding between complementary base pairs." Implicit in this definition are the conditions for achieving specific hybridization to a

nucleic acid having a sequence set forth in SEQ ID NO. 1 or to the complementary sequence of SEQ ID NO. 1. It would be well understood by one skilled in the art at the time the invention was made that conditions for achieving specific hybridization would be conditions that were sufficiently stringent to allow the probe to discriminate between the target sequence and non-PSM antigen gene sequences, and such conditions were known in the art.

Applicants assert that at the time the subject application was filed, it was a routine matter to calculate the melting temperature (T_m) of an oligonucleotide duplex based on the G/C content and length of the oligonucleotide and the ionic strength of the hybridization buffer, and from this T_m value to determine suitable stringent conditions for specific hybridization of the oligonucleotide probe to its target sequence. In support of this assertion, applicants attach hereto as **Exhibit A** pages 11.45-11.49 from Sambrook, Fritsch and Maniatis (1989) "Molecular Cloning: A Laboratory Manual - Second Edition," which describes the determination of hybridization conditions for use with oligonucleotide probes. (The entire Chapter 11 of Sambrook et al. (1989) was previously submitted as Exhibit A to applicants' Amendment In Response To May 12, 1998 Office Action, filed November 12, 1998.) Applicants contend, based upon the teaching of Sambrook et al., that once an oligonucleotide of known sequence and length were selected for use as a hybridization probe, one skilled in the art would be able, without any excessive or undue experimentation, to define appropriate stringent conditions under which the probe would "hybridize

specifically" with a target sequence. Furthermore, as Sambrook et al. point out (Exhibit A, page 11.48), the use of the quarternary alkylammonium salts, tetraethylammonium chloride or tetramethylammonium chloride instead of sodium chloride in the hybridization buffer, renders the T_m of an oligonucleotide hybrid independent of its base composition and dependent primarily on its length. One skilled in the art would recognize that the use of these quarternary alkylammonium salts would make it easier to derive conditions under which a given oligonucleotide probe would specifically hybridize to a target sequence.

Applicants respectfully direct the Examiner's attention to the publication by Hanks ([1987] Homology probing: Identification of cDNA clones encoding members of the protein-serine kinase family. *Proc. Natl. Acad. Sci. USA* 84: 388-392), attached hereto as **Exhibit B**, which was cited in the present specification on page 41, line 10, and was incorporated into the specification by reference to more fully describe the state of the art to which the instant invention pertains (see page 1, lines 20-24 of the specification). In Exhibit B (see page 388, under heading "Library screening with oligonucleotide probe mixtures"), Hanks describes the use of mixed oligonucleotide probes and post-hybridization washes of sequentially increasing stringency (i.e., using a buffer containing 3 M tetramethylammonium chloride and increasing the wash temperature from 42°C to 47°C to 52°C) to progressively select for longer contiguous matches. The Hanks reference, which pre-dates the date to which the subject application claims priority by almost 6 years, clearly indicates that

methods for varying hybridization conditions to permit specific hybridization of oligonucleotide probes were well known to those skilled in the art at the time of the subject invention.

Indeed, examples of hybridization conditions that are sufficiently stringent to permit specific hybridization of nucleic acid molecules to targeted PSM antigen nucleic acid sequences are provided in the present specification. Page 52, lines 23-28, describes northern blot hybridization being performed at 65°C, followed by sequential washes twice each in 1X SSPE/0.5% SDS and 0.1X SSPE/0.5% SDS at 42°C. Similar conditions are also described on page 92, lines 29-33 of the specification, for Southern blot hybridization except that the final two washes are at 50°C.

Applicants also describe hybridization conditions that are sufficiently stringent for the specific hybridization of 20 nucleotide-long nucleic acid primers in the PCR analysis of PSM antigen gene expression in human prostate tissue (see page 52, line 31 to page 53, line 12). Based on the T_m of the primers of 64°C, an annealing temperature of 60°C was used for specific hybridization. Such a condition is known by one skilled in the art to be a stringent condition that insures specificity of the hybridization.

Claims 100-105 and 121 recite nucleic acid probes of at least 15 nucleotides in length that can hybridize specifically to defined nucleic acid target sequences, i.e., probes that can discriminate between targeted PSM antigen gene sequences and

other nucleic acid sequences. The examples cited above from both the present specification and the scientific literature referenced in the specification clearly indicate that one skilled in the art at the time the invention was made could readily determine appropriate conditions for hybridization of nucleic acid probes to insure specificity of duplex formation. Accordingly, applicants respectfully submit that claims 100-105 and 121 satisfy the requirements of 35 U.S.C. §112, second paragraph.

The Examiner also stated that claims 113-115 are confusing because, according to the Examiner, it is unclear whether applicants are referring to the encoded polypeptides of the claimed nucleic acids or to the reference sequence of the outside region of prostate-specific membrane antigen beginning with amino acid number 45 at the amino terminus, when the claims use such phrases as "provided that the polypeptide [or fragment] is characterized by antigenicity" or "which polypeptide is characterized by antigenicity and comprises each of the following sequences..." The Examiner posed the question whether the polypeptides or fragments referred to in these claims were those encoded by the claimed nucleic acids or whether they were the outside region of prostate-specific membrane antigen which is used as the framework to create the claimed nucleic acids.

In response, applicants respectfully traverse the Examiner's rejection. Nevertheless, to expedite the prosecution of this application and without conceding the correctness of the Examiner's position, applicants have amended claims 113-115 to more clearly indicate which polypeptides or fragments have the

properties recited in the claims. Applicants respectfully submit that these amendments obviate the rejection of claims 113-115 under 35 U.S.C. §112, second paragraph, and the Examiner is therefore requested to reconsider and withdraw the rejection.

Claim Rejections under 35 U.S.C. §102(a)

The Examiner rejected claims 100-102, 113-115 and 120-121 under 35 U.S.C. §102(a) as allegedly anticipated by Sulavik et al. ("Sulavik"). According to the Examiner, Sulavik discloses GenBank sequence accession number M89776 (pages 3579 and 3582) whose nucleotides encode amino acids 60-67 of instant SEQ ID NO:2 (citing an attached sequence comparison). The Examiner stated that an eight amino acid peptide is of sufficient length to be antigenic, and he further stated that "this entire sequence" can selectively hybridize to SEQ ID NO:1 under very low stringency conditions since the conditions recited in the instant claims are not defined.

In response, applicants respectfully traverse the Examiner's rejection of claims 100-102, 113-115 and 120-121 under 35 U.S.C. §102(a).

Applicants note that GenBank accession number M89776, which the Examiner cites, discloses a *Streptococcus gordonii* glucosyltransferase (*gtfG*) gene sequence of 1417 bp, and does not specifically teach a sequence encoding the AFLDELKA octapeptide as alleged by the Examiner. Thus, notwithstanding that a small segment (i.e., a 24-mer "species") of the entire

gtfG gene sequence (i.e., the "genus") taught by Sulavik encodes an octapeptide sequence that occurs within the PSM antigen sequence, that small segment cannot be said to anticipate the instant claims because there is absolutely no teaching in Sulavik that identifies the species from among the genus.

Furthermore, applicants assert emphatically that "the entire sequence" of the *S. gordonii gtfG* gene would not "hybridize specifically" to a nucleic acid of the instant claims, i.e., a nucleic acid encoding prostate specific membrane antigen, for at least two reasons.

First, applicants contend that even if the homologous regions in the *gtfG* and PSM antigen genes encoding the shared octapeptide sequence were 100% identical, they would still be too short (24 nucleotides) to permit hybridization between the two genes, considering their otherwise completely divergent sequences. Furthermore, applicants note the relevant 24-mer sequences encoding the same octapeptide in the two genes are actually only 75% identical (6 nucleotide mismatches out of the total 24 nucleotides), and are therefore even less able than fully matched sequences to mediate hybridization.

Second, even if, *arguendo*, the *gtfG* sequence could conceivably hybridize to the PSM antigen gene sequence under very low stringency conditions as stated by the Examiner, the *gtfG* sequence clearly still would not "hybridize specifically" to the PSM antigen gene sequence because it would also hybridize more strongly under these conditions to a variety of other

sequences, including, for example, the glucosyltransferase (*gtfG*) gene itself from *Streptococcus gordonii* and homologous genes from other organisms.

Applicants conclude, therefore, that since the *S. gordonii gtfG* gene sequence disclosed by Sulavik would not hybridize specifically to a nucleic acid encoding PSM antigen as recited in the instant claims, it clearly does not fall within the scope of, and hence does not anticipate, these claims. The Examiner is therefore respectfully requested to reconsider and withdraw his §102(a) rejection of claims 100-102, 113-115 and 120-121 over Sulavik.

Claim Rejections under 35 U.S.C. §102(b)

Claims 100-102, 113-115, and 120-123

The Examiner rejected claims 100-102, 113-115, and 120-123 under 35 U.S.C. §102(b) as allegedly anticipated by Palm et al. ("Palm"). The Examiner stated that Palm discloses the nucleotide sequence of virus SSV1 (pages 244-245) whose nucleotides encode amino acids 62-68 of instant SEQ ID NO:2 (citing an attached sequence comparison). The Examiner further stated that a seven amino acid peptide is of sufficient length to be antigenic and that "this entire sequence" can selectively hybridize to SEQ ID NO:1 under very low stringency conditions since the conditions recited in the instant claims are not defined.

In response, applicants respectfully traverse the Examiner's

rejection of claims 100-102, 113-115, and 120-123 under 35 U.S.C. §102(b).

Applicants note that Palm discloses a virus SSV1 sequence of 15,455 bp, and does not specifically teach a sequence encoding the LDELKAE heptapeptide as alleged by the Examiner. Thus, notwithstanding that a small segment (i.e., a 21-mer "species") of the entire SSV1 genome sequence (i.e., the "genus") taught by Palm encodes a heptapeptide sequence that occurs within the PSM antigen sequence, that small segment cannot be said to anticipate the instant claims because there is absolutely no teaching in Palm that identifies the species from among the genus. Furthermore, applicants assert emphatically emphasize that "the entire sequence" of the SSV1 virus would not "hybridize specifically" to a nucleic acid of the instant claims, i.e., a nucleic acid encoding PSM antigen, for at least two reasons.

First, applicants contend that even if the homologous regions in the SSV1 and PSM antigen gene sequences encoding the shared heptapeptide sequence were 100% identical, they would still be too short (21 nucleotides) to permit hybridization between the two sequences, considering the latter are otherwise completely divergent. Furthermore, applicants note that the relevant 21-mer sequences encoding the same heptapeptide in the two genes are only 71% identical (6 nucleotide mismatches out of the total 21 nucleotides), and are therefore even less able than fully matched sequences to mediate hybridization.

Second, even if, *arguendo*, the SSV1 genome sequence could

conceivably hybridize to the PSM antigen gene sequences under very low stringency conditions as stated by the Examiner, the SSV1 sequence clearly still would not "hybridize specifically" to the PSM antigen gene sequence because it would also hybridize more strongly under these conditions to a variety of other sequences, including, for example, the SSV1 genome itself and the genomes of related viruses.

Applicants conclude, therefore, that since the SSV1 genome sequence disclosed by Palm would not hybridize specifically to a nucleic acid encoding PSM antigen as recited in the instant claims, it clearly does not fall within the scope of, and hence does not anticipate, these claims. The Examiner is therefore respectfully requested to reconsider and withdraw his §102(b) rejection of claims 100-102, 113-115, and 120-123 over Palm.

Claims 100-102, 113-115, and 120-126

The Examiner rejected claims 100-102, 113-115, and 120-126 under 35 U.S.C. §102(b) as allegedly anticipated by Ramakrishnan et al. ("Ramakrishnan"). The Examiner stated that Ramakrishnan discloses the nucleotide sequence of ribosomal protein L18 from *Bacillus stearothermophilus* (page 883) whose nucleotides encode amino acids 101-107 of instant SEQ ID NO:2 (citing an attached sequence comparison (page 883 of the reference) attached at the end of the Office Action). The Examiner contended that a seven amino acid peptide is of sufficient length to be antigenic and that "this entire sequence" can selectively hybridize to SEQ ID NO:1 under very low stringency conditions since the conditions

recited in the instant claims are not defined.

In response, applicants respectfully traverse the Examiner's rejection of claims 100-102, 113-115, and 120-126 under 35 U.S.C. §102(b).

Applicants note that Ramakrishnan discloses the 363 bp nucleotide sequence of ribosomal protein L18 from *Bacillus stearothermophilus*, and does not specifically teach a sequence encoding the KEFGLDS heptapeptide as alleged by the Examiner. Thus, notwithstanding that a small segment (i.e., a 21-mer "species") of the entire L18 gene sequence (i.e., the "genus") taught by Ramakrishnan encodes a heptapeptide sequence that occurs within the PSM antigen sequence, that small segment cannot be said to anticipate the instant claims because there is absolutely no teaching in Ramakrishnan that identifies the species from among the genus. Furthermore, applicants assert emphatically that "the entire sequence" of the L18 gene would not "hybridize specifically" to a nucleic acid of the instant claims, i.e., a nucleic acid encoding prostate specific membrane antigen, for at least two reasons.

First, applicants contend that even if the homologous regions in the L18 and PSM antigen gene sequences encoding the shared octapeptide sequence were 100% identical, they would still be too short (21 nucleotides) to permit hybridization between the two genes, considering their otherwise completely divergent sequences. Furthermore, applicants note the relevant 21-mer sequences encoding the same octapeptide in the two genes are not identical (1 nucleotide mismatch out of the total 21

nucleotides), and are therefore even less able than fully matched sequences to mediate hybridization.

Second, even if, *arguendo*, the *B. stearothermophilus* L18 sequence could conceivably hybridize to the PSM antigen gene sequence under very low stringency conditions as stated by the Examiner, the L18 gene sequence clearly would not "hybridize specifically" to the PSM antigen gene sequence because it would also hybridize more strongly under these conditions to a variety of other sequences, including, for example, the L18 gene sequence itself.

Applicants conclude, therefore, that since the L18 sequence disclosed by Ramakrishnan would not hybridize specifically to a nucleic acid encoding PSM antigen as recited in the instant claims, it clearly does not fall within the scope of, and hence does not anticipate, these claims. The Examiner is therefore respectfully requested to reconsider and withdraw his §102(b) rejection of claims 100-102, 113-115, and 120-126 over Ramakrishnan.

Conclusions

In view of the remarks made herein, applicants respectfully request that the Examiner withdraw the rejection of claims 100-105, 113-115 and 119-126 set forth in the March 12, 2003 Office Action and earnestly solicit allowance of all claims pending in the subject application.

If a telephone interview would be of assistance in advancing

prosecution of the subject application, applicants' undersigned attorneys invites the Examiner to telephone either of them at the number provided below.

No fee, other than the enclosed $205.00 fee for a two-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Mark A. Farley

John P. White
Registration No. 28,678
Mark A. Farley
Registration No. 33,170
Attorneys for Applicant(s)
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Mark A. Farley 8/12/03

John P. White Date
Reg. No. 28,678
Mark A. Farley
Reg. No. 33,170